effective amount of a dematan sulfate or chondroitin sulfate degrading enzyme to decrease fibrous cell proliferative response to growth factors, reduce secretion of collagen by fibroblasts, and thereby decrease the size of fibrous tissue.

Please cancel claims 12-19.

Remarks

Restriction Requirement

Claims 1-19 were divided into two groups, group I, claims to a method of using an enzyme, and group II, claims to an enzyme composition. Applicants affirm their election of group I. Claims 12-19 have been cancelled without prejudice.

Applicants also affirm their election of organ fibrosis and chondroitinase B as the species, with the understanding the generic claims will be examined when the claims to the species are otherwise allowable.

Declaration

A new oath will be submitted shortly.

Rejection under 35 U.S.C. 112

Claims 1-11 were rejected under 35 U.S.C. 112 as indefinite on the basis that the phrase "modulate fibrosis tissue formation" is unclear.

It is believe this term would be understood by those skilled in the art from the ordinary meaning of the words and in view of the specification. However, to faciliate prosecution, the claims have been amended to refer to decreased cell proliferativee response to growth factors, reduced secretion of collagen, and thereby a decrease in the size of fibrous tissue. Support is found at page 3, lines 20-28, for

example.

Rejections under 35 U.S.C. 103

Claims 1-11 were rejected as obvious over U.S. Patent No. 6,153,187 to Yacoby-Zeevi in combination with U.S. Patent No. 5,985,582 to Triscott. These rejections are respectfully traversed if applied to the amended claims.

U.S. patent No. 6,153,187 to Yacoby-Zeevi

Yacoby-Zeevi specifically claims the use of heparinase and heparanase for use in reducing pulmonary disease principally by reducing the viscosity of sputum. In particular this patent addresses the use of aerosolized enzymes to treat the accumulation of very thick sputum found in cystic fibrosis. The only data presented are for heparanase, and that data is confined to showing a reduction in sputum viscosity.

Yacoby-Zeevi does not not address the issue of fibroblast proliferation nor collagen production, as claimed.

U.S. patent No. 5,985,582 to Triscott

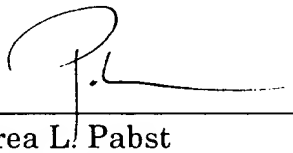
Triscott describes an assay of antithrombin in plasma. No therapeutic uses for treating patients for any disease are suggested nor mentioned. This is an *in vitro* diagnostic assay. Chondroitinases are used, but only in the context of this plasma assay.

Accordingly, one skilled in the art would not be led to treat patients with the claimed enzymes to inhibit proliferation of fibroblasts. Moreover, one would not

have any idea of what an effective amount is, nor how to formulate or administer an effective amount, certainly not with any reasonable expectation of success. See, in contrast, the application at pages 15-21, which not only demonstrates the mechanisms and effective dosages, but also treatment of actual disease in an animal model. Accordingly, claims 1-11 are not obvious over the cited art, alone or in combination.

Allowance of claims 1-11, as amended, is therefore earnestly solicited.

Respectfully submitted,



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APPENDIX: Claims marked as Amended

1. (amended) A method to [modulate] decrease fibrous tissue [formation] size comprising administering to an individual in need of treatment thereof an effective amount of a dematan sulfate or chondroitin sulfate degrading enzyme to decrease fibrous cell proliferative response to growth factors, reduce secretion of collagen by fibroblasts, and thereby decrease the size of fibrous tissue.

2. The method of claim 1 wherein the enzyme is selected from the group consisting of bacterial dermatan or chondroitin sulfate degrading enzyme and is selected from the group consisting of chondroitinase AC from *Flavobacterium heparinum*, chondroitinase B from *Flavobacterium heparinum*, chondroitin sulfate degrading enzymes from *Bacteroides* species, chondroitin sulfate degrading enzymes from *Proteus vulgaris*, chondroitin sulfate degrading enzymes from *Microcossus*, chondroitin sulfate degrading enzymes from *Vibrio* species, chondroitin sulfate degrading enzymes from *Arthrobacter aurescens*, arylsulfatase B, N-acetylgalactosamine-6-sulfatase and iduronate sulfatase from mammalian cells, these enzymes expressed from recombinant nucleotide sequences in bacteria and combinations thereof.

3. The method of claim 1 wherein the enzyme is a mammalian enzyme.

4. The method of claim 1 wherein the enzyme is a bacterial enzyme.

5. The method of claim 4 wherein the chondroitinase is chondroitinase B.

6. The method of claim 1 wherein the individual has a skin disorder.

7. The method of claim 6 wherein the skin disorder is scleroderma or psoriasis.

8. The method of claim 1 wherein the individual has keloid scarring or is at risk of keloid scarring, or has pulmonary fibrosis.

9. The method of claim 1 wherein the enzyme is administered systemically.

10. The method of claim 1 wherein the enzyme is administered topically or locally at or adjacent to a site in need of treatment.

11. The method of claim 1 wherein the enzyme is administered in a controlled and/or sustained release formulation.

Please cancel claims 12-19.

APPENDIX: Clean Copy of Claims as Amended

1. (amended) A method to decrease fibrous tissue size comprising administering to an individual in need of treatment thereof an effective amount of a dematan sulfate or chondroitin sulfate degrading enzyme to decrease fibrous cell proliferative response to growth factors, reduce secretion of collagen by fibroblasts, and thereby decrease the size of fibrous tissue.

2. The method of claim 1 wherein the enzyme is selected from the group consisting of bacterial dermatan or chondroitin sulfate degrading enzyme and is selected from the group consisting of chondroitinase AC from *Flavobacterium heparinum*, chondroitinase B from *Flavobacterium heparinum*, chondroitin sulfate degrading enzymes from *Bacteroides* species, chondroitin sulfate degrading enzymes from *Proteus vulgaris*, chondroitin sulfate degrading enzymes from *Micrococcus*, chondroitin sulfate degrading enzymes from *Vibrio* species, chondroitin sulfate degrading enzymes from *Arthrobacter aurescens*, arylsulfatase B, N-acetylgalactosamine-6-sulfatase and iduronate sulfatase from mammalian cells, these enzymes expressed from recombinant nucleotide sequences in bacteria and combinations thereof.

3. The method of claim 1 wherein the enzyme is a mammalian enzyme.

4. The method of claim 1 wherein the enzyme is a bacterial enzyme.

5. The method of claim 4 wherein the chondroitinase is chondroitinase B.

6. The method of claim 1 wherein the individual has a skin disorder.

7. The method of claim 6 wherein the skin disorder is scleroderma or psoriasis.

8. The method of claim 1 wherein the individual has keloid scarring or is at risk of keloid scarring, or has pulmonary fibrosis.

9. The method of claim 1 wherein the enzyme is administered systemically.

10. The method of claim 1 wherein the enzyme is administered topically or locally at or adjacent to a site in need of treatment.

11. The method of claim 1 wherein the enzyme is administered in a controlled and/or sustained release formulation.

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